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(54) Title: NOVEL ANTISEPTIC DERIVATIVES WITH BROAD SPECTRUM ANTIMICROBIAL ACTIVITY FOR THE IMPREGNATION OF SURFACES

(57) Abstract: The present invention provides novel broad spectrum antiseptic compounds, comprising a basic reagent (such as a guanidium compound, a biguanide, a bipyridine, aphenoxide or an alkyl oxide) bound to a dye, that further have properties that allow them to be coated/impregnated into polymer surfaces. Methods for coating these antiseptic compounds onto medical devices especially in-dwelling medical devices to prevent the growth of pathogens in such devices and hence, to prevent infection to patients via such devices are provided. The invention also provides antiseptics that are useful as general surface disinfectants and sterilizers, fluid disinfectants and biocide preservatives.

DESCRIPTION

NOVEL ANTISEPTIC DERIVATIVES WITH BROAD SPECTRUM ANTIMICROBIAL ACTIVITY FOR THE IMPREGNATION OF SURFACES

BACKGROUND OF THE INVENTION

The present invention claims priority to U.S. Provisional Application Serial No. 60/261,447 filed on January 12, 2001 and U.S. Provisional Application Serial No. 60/316,165 filed on August 30, 2001, which are incorporated by reference in their entirety.

1. Field of the Invention

The present invention relates generally to the fields of preventing infections. More particularly it provides novel broad spectrum antiseptic compositions that further have properties that allow them to be coated/impregnated into polymer surfaces or used as antiseptics in different applications. The invention provides methods for coating these antiseptic compositions onto medical devices such as catheters, tubes, stents and sutures, to prevent the growth of pathogens in such devices and hence, to prevent infection to patients via such devices. In addition, the invention provides novel antiseptics that could be used in disinfecting and sterilizing organic and inorganic surfaces, water and other fluids.

2. Description of Related Art

Most nosocomial infections are caused by the contamination of medical devices resulting in serious hospital-acquired infections. Nosocomial pneumonias are the second most common nosocomial infections, and are associated with the highest attributable mortality and morbidity. Recent data have shown that at least 300,000 episodes of nosocomial pneumonia occur annually in the United States (Official Statement, American Thoracic Society). The attributable mortality of this infection is 33%-50%, hence, around 100,000 patients die annually because of nosocomial pneumonia (CDC, 1993; Leu *et al.*, 1989). The risk of nosocomial pneumonia increases 6- to 20-fold from the use of mechanical ventilation (Official Statement, American Thoracic Society).

The endotracheal tube is considered a common vehicle for colonization/contamination leading to nosocomial pneumonia. The endotracheal tube connects the oropharyngeal environment with the sterile bronchoalveolar space, significantly increasing the risk of nosocomial pneumonia. Endotracheal tubes are typically constructed of polyvinylchloride,

What is needed is an effective antiseptic having broad spectrum activity against resistant staphylococci, vancomycin-resistant enterococci, resistant *Pseudomonas aeruginosa* and *Candida* species, to be used in conjunction with indwelling devices that will inhibit or prevent the nosocomial infections typically associated with the use of these indwelling devices. It would be further desirable to develop devices impregnated with the antiseptic to enhance the resistance to infection. For example, the creation of antiseptic-impregnated catheters would prevent organisms from adhering or migrating on catheter surfaces.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks inherent in the art by providing novel antiseptic derivatives with broad-spectrum activity against various microbes including resistant bacteria and fungi. Methods of preparing these antiseptic compounds and methods for utilizing them are provided.

Therefore, the invention provides an antiseptic composition comprising a basic reagent and a dye. The basic reagent may be bonded to the dye. In one aspect, the basic reagent and the dye are bonded ionically to form the antiseptic compound. In another aspect, the basic reagent and the dye are bonded covalently to form the antiseptic compound. The basic reagent and the dye can be combined in any amount to obtain the antiseptic composition of the invention, however, in a particular embodiment, an equimolar amount of the basic reagent is added to the dye solution. The inventors also contemplate that the antiseptic composition of the invention can be made by combining other amounts of the dye and basic reagent for example, one may combine, in molar ratios, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, 1:25, 1:30, 1:35, 1:40, 1:45, 1:50, 1:55, 1:60, 1:65, 1:70, 1:75, 1:80, 1.85, 1:90, 1:95, to 1:99 of either dye : basic reagent or basic reagent : dye. This includes all the intermediate ranges as well, for example it includes molar ratios such as, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1 and the like for other values listed. It also includes the ranges in between these values such as 1.11:1, 1.12:1 and so on. The skilled artisan will therefore recognize that the dye and basic reagent can be combined in different molar ratio amounts to obtain the antiseptic composition disclosed and that the invention is therefore not limited to any particular molar ratio of dye : basic reagent or basic reagent : dye.

In certain embodiments, the dye can be a triarylmethane dye, a monoazo dye, a diazo dye, an indigoid dye, a xanthene or a fluorescein dye, an anthraquinone dye, or a quinoline dye. In other specific embodiments, the dye is gentian violet, or crystal violet, ethyl violet, brilliant green, an FD&C dye, or a D&C dye. In one example, the FD&C dye is Blue No. 1 or Green No.

In yet other embodiments, the antiseptic compound can coat and/or impregnate an inorganic surface. Examples of such inorganic surfaces include floors, table-tops, counter-tops, surfaces of a hospital equipment, wheelchair surfaces, *etc.* Virtually any surface comprising a material that is capable of being coated by, impregnated with, absorbing or otherwise retaining the antiseptic compounds of the invention may be disinfected and/or sterilized using the present antiseptic compounds and their compositions. Thus, the antiseptic compound of the invention can be used to disinfect, sanitize and sterilize a wide variety of surfaces.

The invention also provides medical devices coated with a basic reagent and a dye. In one aspect the medical devices are coated with a basic reagent and a dye that are ionically bound. In another aspect the medical devices are coated with a basic reagent and a dye that are covalently bound. Examples of medical devices include endotracheal tubes, a vascular catheter, an urinary catheter, a nephrostomy tube, a biliary stent, a peritoneal catheter, an epidural catheter, a central nervous system catheter, an orthopedic device, a prosthetic valve, and a medical implant. The vascular catheter may be a central venous catheter, an arterial line, an pulmonary artery catheter, and a peripheral venous catheter. The central nervous system catheter may be an intraventricular shunt. Other medical devices that can benefit from the present invention include blood exchanging devices, vascular access ports, cardiovascular catheters, extracorpeal circuits, stents, implantable prostheses, vascular grafts, pumps, heart valves, and cardiovascular sutures, to name a few. Regardless of detailed embodiments, applicability of the invention should not be considered limited with respect to the type of medical device, implant location or materials of construction of the device.

The invention also provides methods for coating a medical device with an antiseptic compositions comprising: a) immersing a medical device in a solvent comprising a basic reagent and a dye; b) drying the device; and c) washing off excessive composition. In some embodiments, the solvent used to immerse the device can be methylene chloride, methanol, or a combination thereof.

The invention also provides methods for preventing nosocomial infections in a subject comprising coating a medical device that the subject is required to use with a composition comprising an antiseptic compound comprising a basic reagent bound to a dye. The subject can be human or an animal model.

The type of nosocomial infection that can be prevented by the methods of this invention include, but are not limited to, pneumonia, bacteremia, fungimia, candidemia, a urinary tract infection, a catheter-exit site infection, and a surgical wound infection.

one or more electrons from one atom or group of atoms to another, to create an ionic bond between the basic reagent and the dye comprising an antiseptic compound.

As used herein the specification and claim(s), the words "covalent bonding" or "covalently bound" refers to the chemical bond formed by the sharing of one or more pairs of electrons between the basic reagent and the dye comprising an antiseptic compound.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

A. The Present Invention

Indwelling catheters and other similar implanted medical devices are used routinely in hospitals on a diverse group of patients. A common cause of failure of these medical devices is infection. Pathogens often attach to and proliferate in such devices and eventually invade the patient leading to nosocomial infections. Microorganisms usually migrate along the surfaces of devices to invade sterile environments, such as the bronchoalveolar space leading to pneumonia, the bloodstream leading to bacteremia, or the urinary bladder leading to urinary tract infections.

The present invention provides a series of novel antiseptic compositions with broad-spectrum activity against various nosocomial microorganisms, including resistant bacteria and fungi. For example, the antiseptic compositions are effective against resistant staphylococci, vancomycin-resistant enterococci, resistant *Pseudomonas aeruginosa* and *Candida* species. These novel antiseptics also have unique properties that enable penetration/impregnation of various polymers, such as polyvinyl chloride, polyethylene, silastic elastomers, polytetrafluoroethylene, dacron, collodion, carboethane, nylon, polymers used in the formation of endotracheal tubes, silicone and polyurethane polymers used in the formation of vascular catheters and surgical silk sutures. Thus, they are suitable for coating a wide range of device surfaces.

The inventors demonstrate herein that these novel antiseptics maintain prolonged antimicrobial activity on device surfaces, and thus may be used for the entire lifespan of these indwelling devices. This is an improvement over existing coated or impregnated devices where the

No.	C.I. #	CAS #	No.	C.I. #	CAS #
1	15670	2092-55-9	51	65005	1328-24-1
2	26370	3071-73-6	52	62055	6408-78-2
3	20460	5850-35-1	53	62125	6424-85-7
4	62130	2666-17-3	54	63010	2861-02-1
5	61585	4474-24-2	55	13390	3861-73-2
6	26360	3351-05-1	56	26400	3529-01-9
7	62058	6397-02-0	57	15706	12392-64-2
8	42685	3244-88-0	58	61570	4403-90-1
9	61580	6408-57-7	59	62560	4430-16-4
10	15575	5850-86-2	60	26550	8003-88-1
11	22870	15792-50-4	61	18745	10127-27-2
12	18050	3734-67-6	62	14710	5858-39-9
13	14900	4787-93-3	63	17045	6360-07-2
14	18070	12167-45-2	64	15620	1658-56-6
15	22890	10169-02-5	65	18110	6844-74-2
16	23635	6459-94-5	66	26900	6406-56-0
17	18800	6408-31-7	67	18125	10130-48-0
18	18055	4321-69-1	68	42650	4129-84-4
19	18965	6359-98-4	69	18835	6359-85-9
20	18900	6359-91-7	70	18890	6359-90-6
21	25135	13390-47-1	71	18950	6372-96-9
22	22910	6375-5-9	72	14170	6408-90-8
23	18850	6359-88-2	73	13900	10343-58-5
24	46005:1	494-38-2	74	46025	135-49-9
25		8048-52-0	75	12840	61968-76-1
26	58000	72-48-0	76	63615	1324-21-6
27		3952-78-1	77	58005	130-22-3
28	61710	6408-63-5	78	14025	584-42-9
29	42750	30586-13-1	79	42080	3486-30-4
30		569-58-4	80	16185	915-67-3
31		52417-22-8	81	42780	
32		520-10-5	82		1668-00-4
33	48035	3056-93-7	83	41000	2465-27-2
34		4431-00-9	84	43810	13186-45-3
35	50090	25360-72-9	85	52005	531-53-3
36	52010	531-55-5	86	51004	33203-82-6
37	61111	12217-43-5	87	11075	94233-04-2
38	42500	569-61-9	88	42510	632-99-5
39	11460	42373-04-6	89	48055	4208-80-4
40	23500	992-59-6	90	26905	4196-99-0
41		298-95-3	91		2315-97-1
42	21010	5421-66-9	92	21000	10114-58-6
43		1871-22-3	93	16180	5858-33-3
44	28440	2519-30-4	94	42655	6104-58-1
45	42660	6104-59-2	95		81029-05-2
46	27290	5413-75-2	96	42040	633-03-4
47	24890	3051-11-4	97		102185-52-4
48		76-60-8	98		62625-32-5
49		115-40-2	99		62625-30-3
50		115-39-9	100		62625-28-9
101		14337-53-2	152		16574-43-9
102		76-59-5	153		34722-90-2
103		40070-59-5	154		617-19-6
104		3147-14-6	155	51050	1562-90-9
105	24410	2610-05-1	156		4430-20-0
106	43825	1667-99-8	157	14720	3567-69-9
107	16575	548-80-1	158	16570	4197-07-3
108	43820	3564-18-9	159	11270	532-82-1

219	14010	6054-99-5	270	14045	6470-98-0
220	44530	5715-76-4	271	20470	1064-48-8
221	11350	131-22-6	272	50040	553-24-2
222	16255	2611-82-7	273	42520	3248-91-7
223	52030	6586-05-6	274	51180	3625-57-8
224		7385-67-3	275	14890	5423-07-4
225		74-39-5	276		56431-61-9
226	60760	6409-77-4	277	61555	2646-15-3
227	26120	4477-79-6	278	26125	1320-06-5
228	16230	1936-15-8	279	15510	633-96-5
229	15705	2538-85-4	280	15711	5610-64-0
230	19010	10127-05-6	281	12070	6410-10-2
231	42045	129-17-9	282		143-74-8
232		34487-61-1	283	11000	60-09-3
233		101-75-7	284		16201-96-0
234	11800	1689-82-3	285		975-17-7
235	45410	18472-87-2	286		2768-90-3
236	16680	1058-92-0	287	27195	6226-79-5
237	27190	6226-78-4	288		67627-18-3
238	49000	30113-37-2	289	58205 (75410)	81-54-9
239		16593-81-0	290		115-41-3
240		85531-30-2	291	45010	2150-48-3
241	45005	92-32-0	292		117-92-0
242	58500	81-61-8	293	58050	81-64-1
243	47000	8003-22-3	294	47005	8004-92-0
244	20505	17095-24-8	295	61211	12236-82-7
245	61205	13324-20-4	296	17757	12225-82-1
246	17908	25489-36-5	297	61200	2580-78-1
247		635-78-9	298		123333-76-6
248	45170	81-88-9	299	45170:1	509-34-2
249	45160	989-38-8	300		13161-28-9
250	45440	632-69-9	301	43800	603-45-2
251	50240	477-73-6	302	61554	17354-14-2
252	61552	6994-46-3	303	61565	128-80-3
253		7423-31-6	304	12055	842-07-9
305	12140	3118-97-6	328	26100	85-86-9
306	26105	85-83-6	329	26150	4197-25-5
307	11920	2051-85-6	330	26050	6368-72-5
308		123359-42-2	331		68504-35-8
309		23647-14-5	332		123333-78-8
310	45100	3520-42-1	333	45220	5873-16-5
311	19140	1934-21-0	334		4430-25-5
312		108321-10-4	335		1301-20-8
313		62637-91-6	336		123333-63-1
314		6262-21-1	337		386-17-4
315		632-73-5	338		4430-24-4
316		42798-98-1	339		1719-71-7
317	19540	1829-00-1	340	49005	2390-54-7
318	52000	78338-22-4	341		76-61-9
319		81012-93-3	342		125-20-2
320		123359-43-3	343	52040	92-31-9
321	12120	2425-85-6	344	14270	547-57-9
322	23850	72-57-1	345		14541-90-3
323	44045	2580-56-5	346	44040	2185-86-6
324	42595	2390-60-5	347	45190	6252-76-2
325		125-31-5	348		63721-83-5
326	16150	3761-53-3	349		14936-97-1
327		135-52-4	350		

One example of the novel broad-spectrum antiseptic derivatives of this invention is gendine, which consists of the combination of gentian violet and chlorhexidine. Gentian violet, on its own, is a good impregnating triarylmethane dye. Bhatnager *et al.*, 1993 have shown in an *in vitro* study that gentian violet alone can be used to impregnate the surface of CSF silicone shunts and prevent the colonization of *S. epidermis* on these surfaces. However, after impregnating the surfaces of various polymers, including polyvinylchloride, gentian violet on its own has no activity against *Pseudomonas aeruginosa*, which is the second most common cause of nosocomial pneumonia and the third most common cause of nosocomial urinary tract infections. Antiseptics such as chlorhexidine cannot attach on their own onto the surfaces of polyvinylchloride tubes or silicone catheters and silk sutures. They require an impregnating vehicle. Furthermore, on their own they are not highly active against *Pseudomonas aeruginosa*. On the other hand, upon the binding of gentian violet with chlorhexidine, the new antiseptic agent synthesized, is a potent and effective broad-spectrum antiseptic and has the additional ability to coat/impregnate various device surfaces. Gendine is unique in its ability to impregnate various device polymers, such as polyvinylchloride used in the formation of endotracheal tubes, silicone and polyurethane polymers used in the formation of vascular, as well as peritoneal, epidural, urinary and intraventricular catheters. In addition, gendine is able to impregnate the silk sutures used in surgical wounds.

In addition to **Gendine**, other antiseptics encompassed by this invention are **Genlenol** and **Genfoctol**.

The invention also provides methods to generate a wide variety of antiseptic medical devices. Some examples include antiseptic endotracheal tubes, antiseptic vascular catheters, including central venous catheters, arterial lines, pulmonary artery catheters, and peripheral venous catheters, antiseptic urinary catheters, antiseptic nephrostomy tubes, antiseptic biliary stents, antiseptic peritoneal catheters, antiseptic epidural catheters, antiseptic central nervous system catheters, including intraventricular shuts and devices, antiseptic prosthetic valves, orthopedic implants and antiseptic sutures.

B. Pathogens

The nosocomial bacterial infections result in diseases such as bacteremia, pneumonia, meningitis, osteomyelitis, endocarditis, sinusitis, arthritis, urinary tract infections, tetanus, gangrene, colitis, acute gastroenteritis, bronchitis, and a variety of abscesses, and opportunistic infections. Bacterial pathogens include Gram-positive cocci such as *Staphylococcus aureus*, coagulase negative staphylocci such as *Staphylococcus epidermis, Streptococcus pyogenes* (group A), *Streptococcus spp.* (viridans group), *Streptococcus agalactiae* (group B), *S. bovis,*

examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Synthesis of Gendine and Impregnation of Devices

Impregnation Procedure

The general procedure involves, and when applicable, prior preparation of the basic reagent (such as chlorhexidine) in anhydrous solvent, addition of the basic reagent to a solution of a dye (such as Gentian violet) in anhydrous solvent (or addition of the dye to the basic solution), stirring the resulting mixture for 30-90 minutes at ambient conditions, evaporating the solvent also under ambient conditions, and finally dissolution of the residue prior to impregnation. The following procedure illustrates impregnation with Gendine, an example for employing a basic guanidium derivative (*e.g.*, chlorhexidine) and triarylmethane dye (*e.g.*, Gentian violet).

Potassium *tert*-butoxide in THF, 7.35 ml of 1M solution, was added to a solution of CHX diacetate, 1.533 g; 2.45mmol in 35 ml THF. The resulting heterogeneous solution was stirred for 20 minutes, then added to a solution GV, 1.0 g; 2.45 mmol, in 30 ml THF (GV used as an example of Triarylmethane Dye). The mixture was stirred at ambient conditions for 1 hour, then placed under the hood overnight to evaporate the solvent. The resulting residue was dissolved in 30 ml DCM (or MeOH). When applicable, the base (such as neutral form of chlorhexidine) is added to a stirring solution of dye (such as GV) in DCM and the resulting mixture is stirred for at least 1 h. With anionic dyes, dissolution is achieved with the addition of at least one equivalent of a quaternary amine (such as tetraethylammonium) prior to addition of the base. One-centimeter device segments were immersed in the DCM solution for the appropriate period, generally PVC and PU for 10 minutes; Silicone (Si) and Silk Suture for 2 hours. The devices were removed from the solution, and traces of solution were removed from the lumen when applicable. The impregnated devices were placed under the hood to dry for at least 4 hours, preferably over night, then washed with distilled water until the washings were colorless or very faint, and finally placed under an aseptic hood to dry under ambient conditions for at least 4 hours, preferably overnight.

TABLE 3

Endotracheal PVC Tubes, (7.0 mm I.D.)

	Zones of Inhibition (in mm) obtained for		
Reagent in MeOH	*MRSA*$_{2066}$	*PS*$_{4205}$	*C. Parap.*$_{1\text{-}100\text{-}0022}$
GV[†]	20:21	0:0	18:19
CHX[†]	0:0	0:0	0:0
GN[†]	24:25	13:13	23:23

[†]Device immersed for 2 hours.

As shown in Tables 2 and 3, endotracheal PVC tubes impregnated with Gendine (GN) are far more effective against all organisms when compared with those impregnated with CHX, and more effective than PVC tubes impregnated with GV against *Pseudomonas aeruginosa*.

TABLE 4

Double lumen 10.0 FR-Cook Silicone Catheter

	Zones of Inhibition (in mm) obtained for		
Reagent in DCM	*MRSA*$_{2066}$	*PS*$_{4205}$	*C. Parap.*$_{1\text{-}100\text{-}0022}$
GV[†]	6:7	0:0	0:0
CHX[†,§]	0:0	0:0	0:0
GN, 1st trial[†]	18:19	11:12	19:19
GN, 2nd trial[†]	19:19 (19:20)[‡]	10:11 (12:13)[‡]	18:18 (24:25)[‡]

MRSA = Methicillin-Resistant *Staphylococcus aureus*.
PS = *Pseudomonas aeruginosa*
C. Parap. = *Candida Parapsilosis*
[§]DCM solution containing about 33% MeOH $_{v/v}$.
[†]Device immersed for 2 hours.
[‡]Values between parenthesis are for 20 hour immersions.

Again data in Table 4 shows how silicone catheters impregnated with GN are more effective in inhibiting *MRSA, PS* and *C. parapsilosis* than catheters impregnated with either GV or CHX.

common gram-negative bacterium found in nosocomial infections. They are intrinsically more resistant than gram-positive bacteria to many antiseptics, particularly when present in a biofilm or when associated with a device infection (Platt *et al.*, 1988).

For PVC and silicone (Si) devices, this invention shows no activity against *Pseudomonas aeruginosa,* when impregnated with either the immobilizing dye (gentian violet) or CHX alone. All devices impregnated with GN exhibit fair to good activity against *Pseudomonas aeruginosa.* This is important especially since *Pseudomonas aeruginosa* is responsible for 16% of nosocomial pneumonia cases (and is considered by the Centers for Disease Control as the second most common cause of nosocomial ventilator associated pneumonia), 12% of nosocomial urinary tract infections, 8% of surgical wound infections, and 10% of nosocomial bloodstream infections (Van Delden and Iglewski, 1998).

Staphylococcal resistance to antiseptics are known worldwide (Russel A. D., 1997). In addition to CHX, low-level resistance to three antiseptics (acriflavin, benzalkonium chloride, and hexamidine diisethionate is documented (Reverdy *et al.*, 1992; Townsend *et al.*, 1985; Heir *et al.*, 1995). The present study reveals that all GN-impregnated devices, including sutures, exhibit significant biocidal activity against methicillin-resistant staphylococci. This finding is extremely important in light of the fact that methicillin-resistant staphylococci (MRSA and MRSE) are the leading causes of device-related infections, including vascular catheter-related bacteremia and surgical wound infections. In addition *S. aureus* is one of the leading causes of nosocomial pneumonia (Klempner *et al.*, 1998).

The effectiveness of gendine-impregnated devices against *Candida* is no less noteworthy. As revealed from this study, silicone catheter and suture impregnated with GN exhibit fair to good activity against *C. Parapsilosis,* which is not the case for either GV or CHX-impregnated devices. Catheter-related candidemia is now the third leading cause of vascular catheter-related bloodstream infections (Raad *et al.*, 1992). In addition, candidemia in severely immunocompromised patients (i.e., HIV, bone-marrow recipients and leukemia patients) is an important cause for morbidity and mortality and catheters are a major source for this infection (Tumbarello *et al.*, 1998; Gonzalez *et al.*, 1996; Lecciones *et al.*, 1992; Wey *et al.*, 1989). The known chlorhexidine-sulfadiazine impregnated catheters and the minocycline-rifampin impregnated catheters do not have significant prophylactic effect against fungi (Tacconelli *et al.*, 1997; Raad *et al.*, 1997).

TABLE 8

Zones of Inhibition (in mm) imparted by Silicone catheters[f]

	Zones of Inhibition (in mm) against		
Reagent	*MRSA*$_{2066}$	*Alcaligenes faecalis*$_{3681}$	*C. Parap.*$_{1\text{-}100\text{-}0022}$
GV[†]	6:7	0:0	0:0
PCMX[‡]	0:0	0:0	0:0
GV[+].PCMX[-*]	16:16	0:0	16:16
CFTL[§]	0:0	0:0	0:0
GV[+].CFTL[-¶]	20:20	10:10	28:29

[f]Double lumen 10.0 FR-Cook Silicone catheter. [†]Gentian violet. [‡]Chloroxylenol. [*]Genlenol.[§] Clofoctol. [¶]Genfoctol.

TABLE 9

Zones of Inhibition (in mm) imparted by Polyurethane catheters[f]

	Zones of Inhibition (in mm) against		
Reagent	*MRSA*$_{2066}$	*Alcaligenes faecalis*$_{3681}$	*C. Parap.*$_{1\text{-}100\text{-}0022}$
GV[†]	22:22	18:18	22:23
PCMX[‡]	0:0	0:0	0:0
GV[+].PCMX[-*]	24:24	18:20	31:31
CFTL[§]	0:0	0:0	0:0
GV[+].CFTL[-¶]	23:23	15:17	30:32

[f]Double lumen 10.0 FR-catheter. [†]Gentian violet. [‡]Chloroxylenol. [*]Genlenol.[§] Clofoctol. [¶]Genfoctol.

TABLE 10

Zones of Inhibition Imparted by Silk Sutures

	Zones of Inhibition (in mm) against	
Reagent	*MRSA*$_{2066}$	*C. Parap.*$_{1\text{-}100\text{-}0022}$
GV[†]	8:8	0:0
PCMX[‡]	0:0	0:0
GV[+].PCMX[-*]	11:11	5:5
CFTL[§]	0:0	0:0
GV[+].CFTL[-¶]	17:17	15:16

[†]Gentian violet. [‡]Chloroxylenol. [*]Genlenol.[§] Clofoctol. [¶]Genfoctol.

In general, many other gentian violet basic preparations significantly affect the efficacy and biocidal activity of coated sutures and silicone-impregnated catheters against MRSA and *C. Parapsilosis*. Some examples are shown below in Table 11.

Tests that will be used to monitor the effectiveness of the treated medical device include: physical exam, X-ray, blood work and other clinical laboratory methodologies used to detect pathogens in the patients and also methods to detect presence of pathogens in the medical device. Described below is a study guideline for patients using central venous catheters.

A. Efficacy of Central Venous Catheters Coated with Antiseptics of the Invention

Patient Eligibility. Patients will be recruited from intensive care units, bone marrow transplant and melanoma services and other hospital divisions where catheters are used routinely on inpatients. Patients who require a new insertion of a central venous catheter (CVC) and have none of the exclusion criteria will be approached to obtain informed consent. The exclusion criteria are the following:

1. Age <18 years
2. Dermatitis over catheter insertion site
3. Pregnancy
4. Allergy to chlorhexidine or gentian violet
5. Expected duration of catheter placement <3 days
6. Inability to obtain informed consent

The eligible consenting patient will be informed that the catheter to be inserted has either been coated with an antiseptic compound (for example Gendine) or has not been coated, but the subject will not be informed as to whether the specific catheter to be inserted contains the compound.

Each female with child bearing potential will have a urine sample prior to catheter placement to test for pregnancy (if appropriate).

Catheter insertion. Catheters will be inserted into a subclavian vein or internal jugular vein using gown, mask, sterile gloves and full sterile drapes. Skin will be prepped using povidone iodine allowing 1 minute of exposure time. After insertion, the catheter will be secured to the skin using tape and the skin puncture site will be covered with povidone-iodine ointment. Then, the insertion site and the surrounding area will be covered with sterile gauze and taped securely.

Catheter maintenance. Catheters will be inspected every 72 hrs for evidence of site infection (erythema around catheter, purulent drainage, swelling tenderness over catheter). Every 72 hrs (or sooner if necessary) the dressing will be removed and the exit site will be re-

6. Positive blood cultures that are thought to be clinically significant (i.e. associated fever, increased WBC) and no other site of infection is identifiable.

When the patient becomes febrile, blood will be withdrawn simultaneously through the lumen of the catheter and peripheral vein for quantitative blood culture. At the time of catheter removal, the catheter will be removed under aseptic conditions and the tip and intracutaneous segments saved for culturing using the roll plate and sonication quantitative catheter culture technique. At the time of removal each lumen will be marked as to its prior use (hyperalimentation).

Patient Evaluation

1. **Pre-insertion evaluation.** Pertinent history will be taken and physical examination will be done regarding inclusion and exclusion criteria. Demographic data as well as details pertaining to underlying malignancy, treatment and antimicrobial treatment (including antimicrobial prophylaxis for infections in general in patients with hematologic malignancies) will be recorded. Investigational nature of study will be explained and informed consent will be obtained from patient. Pregnancy tests (serum or urine) will be obtained on all female patients with child bearing potential. If the test is positive, the patient will be excluded.

Initial catheterization procedure details will be recorded including catheter type, site and date of placement; difficulty of insertion, and complications if any. The difficulty of insertion will be determined by noting the following (a) number of attempts to insert the catheter (b) time spent during insertion (c) malpositioning and repositioning of a catheter.

2. **Post-insertion evaluation.** All patients will be monitored until the catheter is removed. Catheter site evaluation will be undertaken every 72 hrs with the change of dressing. Special attention will be given to erythema, infiltration, pain, tenderness, swelling, suppuration, palpable cord in vessel, tissue warmth, lymphangitis or phlebitis. Details pertaining to chemotherapy, antineoplastic and antimicrobials, will be recorded. Catheter usage as for agents that might cause sclerosis of the vessel involved, hyperalimentation, blood and blood products administration, and drawing of blood will be noted. The catheter insertion site will be recorded on every patient. In addition, events of repositioning the catheter after displacement will be recorded. Microbiologic evaluation of insertion site will be undertaken in the form of site cultures if suppuration is present. If catheter related septicemia is suspected, blood cultures will be drawn simultaneously through catheter and by peripheral venipuncture. Another set of cultures will be drawn 24 hours later. If thrombophlebitis is suspected venous flow study of

compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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15. The antiseptic composition of claim 6, wherein the monoazo dye is FD&C Yellow No. 5 or FD&C Yellow No. 6.

16. The antiseptic composition of claim 7, wherein the diazo dye is D&C Red No. 17.

17. The antiseptic composition of claim 8, wherein the indigoid dye is FD&C Blue No. 2.

18. The antiseptic composition of claim 9, wherein the xanthene dye is FD&C Red No. 3.

19. The antiseptic composition of claim 10, wherein the anthraquinone dye is D&C Green No. 6.

20. The antiseptic composition of claim 11, wherein the quinoline dye is D&C Yellow No. 1.

21. The antiseptic composition of claim 1, wherein the basic reagent is a guanidium compound, a biguanide, a bipyridine, a phenoxide antiseptic, an alkyl oxide, an aryl oxide, a thiol, a halide, an aliphatic amine, or an aromatic amine.

22. The antiseptic composition of claim 21, wherein the basic reagent is a guanidium compound.

23. The antiseptic composition of claim 22, wherein the guanidium compound is chlorhexidine.

24. The antiseptic composition of claim 22, wherein the guanidium compound is alexidine.

25. The antiseptic composition of claim 22, wherein the guanidium compound is hexamidine.

26. The antiseptic composition of claim 21, wherein the basic reagent is a bipyridine.

27. The antiseptic composition of claim 26, wherein the bipyridine is octenidine.

39. The antiseptic compound of claim 36, wherein said surface is composed of silicone.

40. The antiseptic compound of claim 36, wherein said surface is a silk suture.

41. The antiseptic compound of claim 36, wherein the surface is an organic surface.

42. The antiseptic compound of claim 41, wherein the organic surface is skin.

43. The antiseptic compound of claim 41, wherein the organic surface is a mucosal surface.

44. The antiseptic compound of claim 41, wherein the organic surface is a wound.

45. The antiseptic compound of claim 36, wherein the surface is an inorganic surface.

46. The antiseptic compound of claim 45, wherein the inorganic surface is a floor.

47. The antiseptic compound of claim 45, wherein the inorganic surface is a table-top.

48. The antiseptic compound of claim 45, wherein the inorganic surface is a counter-top.

49. The antiseptic compound of claim 45, wherein the inorganic surface is the surface of a hospital equipment.

50. The antiseptic compound of claim 45, wherein the inorganic surface is a wheelchair surface.

51. A medical device coated with a basic reagent and a dye.

52. The medical device of claim 50, wherein a basic reagent and a dye are bonded.

53. The medical device of claim 52 wherein the basic reagent and the dye are bound ionically.

63. The method of claim 60, wherein said nosocomial infection is caused by a bacterium.

64. The method of claim 63, wherein said bacterium is a resistant bacterium.

65. The method of claim 64, wherein said resistant bacterium is selected from a group comprising methicillin-resistant staphylococci, vancomycin-resistant enterococci, and resistant *Pseudomonas aeruginosa*.

66. The method of claim 60, wherein said nosocomial infection is caused by a fungus.

67. The method of claim 66, wherein said fungus is a resistant fungus.

68. The method of claim 67, wherein said resistant fungus belongs to *Candida species*.

69. A method for disinfecting and/or sterilizing a surface comprising applying a composition comprising a basic reagent and a dye of claim 1 to the surface.

70. The method of claim 69, wherein the surface is an organic surface.

71. The method of claim 70, wherein the organic surface is selected from a group comprising, skin, a mucosal surface, and a wound surface.

72. The method of claim 69, wherein the surface is an inorganic surface.

73. The method of claim 72, wherein the inorganic surface is selected from a group comprising a floor, a table-top, a counter-top, hospital equipment, a wheel chair, gauze, cotton.

74. A method for disinfecting and/or sterilizing a fluid comprising adding a composition comprising a basic reagent and a dye of claim 1 into the fluid.

75. The method of claim 74, wherein said fluid is water.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/00781

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N47/44 A01N43/38 A01N43/90 A01N43/42 A01N43/16
A01N43/20 A01N33/26 A01N33/06 A01N33/04 A01N31/16
A01N31/08 A01N43/40 A01N31/12 A61L2/16 A61L29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 635 652 A (STRECK CLEMENS) 18 January 1972 (1972-01-18) column 2, line 10-17 column 5, line 17-35 column 5, line 54 -column 6, line 70	1-7, 10-16, 19-23
X	EP 1 044 686 A (GILBERT SA LAB) 18 October 2000 (2000-10-18) paragraphs '0009!-'0014!,'0027!	1-3,11, 20-25, 32,33, 36-50, 69-71

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 5 811 471 A (SHANBROM EDWARD) 22 September 1998 (1998-09-22) column 2, line 10-58 column 4, line 49-55	1-79
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/00781

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